REMARKS

Claims 1, 5, 9, 12, 53, 54, 60, and 61 are pending. Claims 1 and 12 are amended herein to more clearly set forth aspects of the invention. Accordingly, instant claims 1, 5, 9, 12, 53, 54, 60, and 61 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for the amendment to claims 1 and 12 is presented, for example, at paragraphs [0004], [0006], [0008], [0079], wherein support for practicing the method of the invention in a mammal in an adjuvant setting is found. No issue of new matter is introduced by the amendments to the claims.

Rejections under 35 USC § 102

Claims 1, 5, 9, 12, 53, 54, 60, and 61 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Varner [United States Patent Number (USPN) 7,311,911]. In view of the amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1, 5, 9, 12, 53, 54, 60, and 61, is respectfully traversed.

The claims are amended herein to be directed to a method for disrupting survival signaling from a bone marrow microenvironment to single breast cancer cells or breast cancer cell micrometastases in a mammal with breast cancer, said method comprising administering to said mammal with breast cancer (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of single breast cancer cells or breast cancer cell micrometastases in a mammal with breast cancer or for treating a single breast cancer cell or breast cancer micrometastases in a mammal with breast cancer comprising administering to the mammal with breast cancer (claim 12), either of said methods comprising administering as adjuvant therapy an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin. This amendment clarifies the timing of administration of the agent of the invention to an adjuvant setting and, in so doing, defines the patient population to be treated as breast cancer patients who have received previous treatment to eliminate detectable disease. Such patients have no detectable disease, but are treated

with adjuvant therapy to prevent relapse of disease. See, for example, paragraphs [0004], [0006], [0008], and [0079] of the instant specification for additional details.

As described in the instant application, breast cancer cells metastasize to the bone marrow early in the course of the disease, wherein most of these cells die. Some well-differentiated breast cancer cells are, however, capable of surviving in the marrow microenvironment and remain dormant, or growth arrested therein without loss of viability, for years. They remain protected from death and, in fact, survive multiple rounds of adjuvant chemotherapy administered specifically to eradicate them. The factors and mechanisms that induce dormancy, that is, growth arrest coupled with long-term survival, of occult breast cancer cells in the bone marrow microenvironment and which protect the cells from chemotherapy were largely unknown prior to the discovery of the present inventor. See, for example, paragraphs [0004] and [0008] of the instant application. More particularly, the present invention relates to the novel finding that increased expression of integrins alpha-5 and beta-1 on metastasized breast cancer cells in the bone marrow transmits a survival signal from matrix proteins in the bone marrow. The present inventor determined that ligation of the integrins initiates the cell survival signaling that leads to dormancy, protection from adjuvant chemotherapy and ultimately relapse in the breast cancer patient. Accordingly, the method of the invention is directed to blocking this survival pathway that enables well differentiated metastatic breast cancer cells to remain dormant and resistant to therapeutic modalities in an adjuvant setting. See, for example, paragraph [0079] of the instant application.

For the sake of clarity, the term adjuvant therapy is a term of the art and is defined as a treatment or treatments administered to a patient in the absence of detectable disease. As detailed, for example, in the website provided by Cancer Research UK, entitled "How a cancer spreads" (hard copy attached hereto; submitted as Exhibit A), after removal of the primary tumor by surgical resection, micrometastases may be present. Under such circumstances, "*If the doctor thinks it is likely that there are micrometastases, they may offer further treatment with chemotherapy, radiotherapy or hormone therapy. This is called 'adjuvant treatment'. The aim is to kill the cancer deposits before they grow big enough to be seen on a scan.*" A copy of a review article by Fisher (Cancer Res. 68:10007-10020, 2008; submitted as Exhibit B), which details the evolution of medical

intervention for the treatment of cancer, is also attached for the Examiner's consideration. The section entitled "Advent of systemic therapy as an adjunct to surgery (1972)" is particularly noteworthy with regard to the term adjuvant therapy. As stated therein, "The treatment of patients who had no identifiable metastatic disease with systemic adjuvant therapy because of the possibility that in the future they might develop distant disease was a revolutionary departure from previous strategies." See page 10016, right column, last sentence of first paragraph under the indicated header. In light of the above, "adjuvant therapy" is a well established term in the art with a defined meaning and such therapy has been used effectively in clinical settings for over thirty years.

Moreover, in keeping with the above definition of adjuvant therapy, adjuvant chemotherapy is defined in the website provided the American Cancer Society (submitted as Exhibit C) as follows:

> *"**Adjuvant chemotherapy:** Systemic therapy given to patients after surgery who have no evidence of cancer spread is called adjuvant therapy. When used as adjuvant therapy after breast-conserving surgery or mastectomy, chemotherapy reduces the risk of breast cancer coming back.*
>
> *Even in the early stages of the disease, cancer cells may break away from the primary breast tumor and spread through the bloodstream. These cells don't cause symptoms, they don't show up on imaging tests, and they can't be felt during a physical exam. But if they are allowed to grow, they can establish new tumors in other places in the body. The goal of adjuvant chemotherapy is to kill undetected cells that have traveled from the breast."* Emphasis added.

It is also noteworthy that the term micrometastases is an accepted term in the art of medical oncology and is defined in the Cancer Research UK website (Exhibit A), for example, as follows: "Micrometastases are metastases (cancer spread) that are too small to be seen. If there are individual cells, or even small areas of growing cells elsewhere in the body, there is no scan detailed enough to spot them." This definition is essentially reiterated in the website provided by the NCI Dictionary of cancer terms (submitted as

Exhibit D), wherein micrometastases are defined as "Small numbers of cancer cells that have spread from the primary tumor to other parts of the body and are too few to be picked up in a screening or diagnostic test."

In light of the above, the instant claims are directed to a method of treating a patient population, wherein the timing of administration is explicitly defined as being performed as adjuvant therapy. In that the administering is provided in an adjuvant setting, the patient population, by definition, has no detectable disease. This stands in marked contrast to Varner which provides a method of reducing the severity of a pathological condition associated with angiogenesis in an individual, by administering to the individual an agent that interferes with specific binding of α5β1integrin to a ligand in a tissue associated with the pathological condition, thereby reducing or inhibiting angiogenesis in the tissue and, consequently, reducing the severity of the pathological condition. The condition can be any pathological condition associated with angiogenesis, including a neoplasm, which can be a malignant neoplasm, for example, a carcinoma such as breast carcinoma, colon carcinoma, ovarian carcinoma or pancreatic carcinoma, or a sarcoma, mesothelioma, teratocarcinoma, an astrocytoma, glioblastoma, or other neoplasm, including a metastatic malignant neoplasm. See column 4, lines 13-27. It is, therefore, apparent that Varner is directed to a method of treating a patient with detectable disease, namely a pathological condition associated with angiogenesis. Recitation in the instant claims that the agent is administered as adjuvant therapy specifies the timing of administration and defines the patient population of the present invention as having no detectable disease. In that Varner fails to teach or suggest administration of an agent as adjuvant therapy or treatment of a patient population without detectable disease, this reference is deficient with regard to at least these elements of the instant claims.

That being the case, the Varner reference fails to teach each and every recited element of the claims. Moreover, the Varner reference also fails to provide any motivation to attempt the claimed method.

In view of the amendments to the claims and arguments presented herein, therefore, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

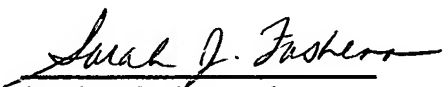
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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February 12, 2008

Enclosures: Petition for a Three Month Extension of Time
Exhibits A-D

EXHIBIT A

CANCER RESEARCH UK

How a cancer spreads

This page tells you about how a cancer spreads. There is information about

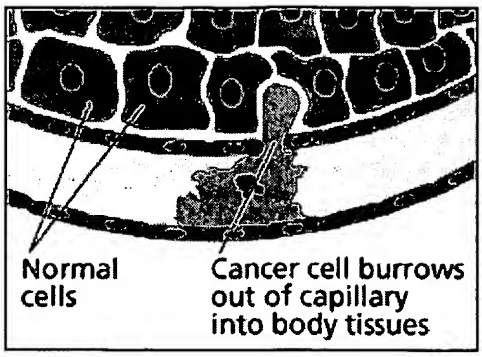
Primary and secondary cancer
The main reason cancer can be difficult to cure is that it can spread to a different part of the body from where it started. The cancer that grows where it first started in the body is called the 'primary cancer'. The place a cancer spreads to and then starts growing is called the 'secondary cancer' or 'metastasis'.

How a cancer spreads
In order to spread, some cells from the primary cancer must break away, travel to another part of the body and start growing there. Cancer cells do not stick together as well as normal cells. They also may produce substances that stimulate them to move. But how do cancer cells travel through the body?

There are three main ways a cancer spreads

Local spread
The cancer grows directly into nearby body tissues. There is more about this in the page on how cancers grow.

Through the blood circulation
In order to spread, the cancer cell must first become detached from the primary tumour. It must then slip through the wall of a blood vessel to get into the bloodstream.



When it is in the bloodstream, it is swept along by the circulating blood until it gets stuck somewhere, usually in a very small blood vessel called a capillary.

Then it must slip through the wall of the capillary and into the tissue of the organ close by. There it must start to multiply to grow a new tumour.

As you can see, this is a complicated journey. Most cancer cells do not survive it. Probably, out of many thousands of cancer cells that reach the blood circulation only one will survive to form a secondary cancer or metastasis.

Some cancer cells are probably killed off by the white blood cells in our immune system. Others cancer cells may die because they are battered around by the fast flowing blood.

Cancer cells in the circulation may try to stick to platelets to form clumps to give themselves some protection. This may also help them to be filtered out in the next capillary network they come across so they can then move into the tissues to start a secondary tumour.

Through the lymphatic system

The way a cancer spreads through the lymphatic system is very similar to the way it spreads through the bloodstream. The cancer cell must become detached from the primary tumour. Then it travels in the circulating lymph fluid until it gets stuck in the small channels inside a lymph node. There it begins to grow into a secondary cancer.

Why cancers spread where they do

Whether it is in the blood or the lymph, the spreading cancer cell stops at the first place it gets stuck. In the bloodstream, this is often the first capillary network it comes across. The blood flow from most body organs goes next through the capillaries in the lungs. So not surprisingly, the lungs are a very common place for cancer to spread to.

The blood from the organs of the digestive system goes through the capillaries of the liver before going back to the heart and then to the lungs. So it is common for digestive system

cancers to spread to the liver. In fact, the liver is the second most common area of cancer spread.

Some cancers show unexpected patterns of spread. For example, prostate cancer often spreads to the bones. Scientists are still investigating why this happens.

During cancer surgery, it is routine for the surgeon to remove the main lymph nodes close to the area of the cancer. For example, the surgeon operating to remove a breast cancer will remove at least some of the lymph nodes from under the arm. These are the first lymph nodes through which lymph draining from the breast flows. The surgeon does this because the first lymph nodes draining an organ are the most likely ones to contain cancer cells.

Micrometastases

Micrometastases are metastases (cancer spread) that are too small to be seen. If there are individual cells, or even small areas of growing cells elsewhere in the body, there is no scan detailed enough to spot them.

For a few tumours, blood tests can detect proteins released by the cancer cells. These may give a sign that there are metastases too small to show up on a scan. But for most cancers, there is no blood test that can say whether a cancer has spread or not.

For most cancers the doctor can only say whether it is **likely** or not that a patient has micrometastases. This 'best guess' may be based on

- Previous experience of many other patients treated in the same way. Doctors naturally collect and publish this information to help each other.
- Whether cancer cells are found in the blood vessels in the tumour removed during surgery (for example in testicular cancer). If they are found then cancer cells are more likely to have reached the bloodstream and spread to somewhere else in the body.
- The grade of the cancer – the higher the grade, the more aggressive the cancer and the more likely that cells have spread.
- Whether lymph nodes that were removed at operation contained cancer cells (for example in breast cancer or bowel cancer). This is direct evidence that cancer cells have broken away from the original cancer. But there is no way of knowing whether any have spread further.

This information is important. If the doctor thinks it is likely that there are micrometastases, they may offer further treatment with chemotherapy, radiotherapy or hormone therapy. This is called 'adjuvant treatment'. The aim is to kill the cancer deposits before they grow big enough to be seen on a scan.

Some doctors call this 'belt and braces' treatment. In other words, the treatment is to try to make sure the cancer does not come back. No one can know for sure if all the cancer cells have been destroyed when someone has finished treatment. It is this uncertainty that can make cancer difficult to cope with for many people, even if they seem to have been successfully treated.

Last updated 19 December 2008

EXHIBIT B

Biological Research in the Evolution of Cancer Surgery: A Personal Perspective

Bernard Fisher

University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

During the 19th, and for most of the 20th century, malignant tumors were removed by mutilating radical anatomic dissection. Advances such as anesthesia, asepsis, and blood transfusion made possible increasingly more radical operations. There was no scientific rationale for the operations being performed. Surgery in the 20th century was dominated by the principles of William S. Halsted, who contended that the bloodstream was of little significance as a route of tumor cell dissemination; a tumor was autonomous of its host; and cancer was a local-regional disease that spread in an orderly fashion based on mechanical considerations. Halsted believed that both the extent and nuances of an operation influenced patient outcome and that inadequate surgical skill was responsible for the failure to cure. A new surgical era arose in 1957, when cancer surgery began to be influenced by laboratory and clinical research, with results contrary to Halstedian principles. A new hypothesis resulted in a *scientific basis* for cancer surgery. Clinical trials supported the thesis that operable cancer *is* a systemic disease and that variations in local-regional therapy are unlikely to substantially affect survival. Complex host-tumor relationships were shown to affect every aspect of cancer and, contrary to Halsted's thesis, the bloodstream is of considerable importance in tumor dissemination. Clinical trials also have shown that less radical surgery is justified. Studies have shown that improved survival can be achieved with systemic therapy after surgery. Such therapy can reduce both the incidence of distant disease and the tumor recurrence at the tumor site after minimal surgery. The use of systemic therapy in patients who have no identifiable metastatic disease is a drastic departure from previous strategies. New technological innovations resulting from engineering research have improved the quality of life of patients by eliminating the need for some surgical procedures. Because cancer is apt to be a systemic disease, however, clinical trials are necessary to determine the effect of these modalities on patient outcome. Although technological developments will continue to play a role in cancer therapy, research in molecular biology and genetics will dictate the future status of cancer treatment and, ultimately, the future of surgery. [Cancer Res 2008;68(24):10007–20]

Introduction

It is of historic interest that the American Association for Cancer Research (AACR) was founded by four surgeons, five pathologists, one chemist, and a biochemist at the 25th meeting of the American Surgical Association in Washington, DC, on May 7, 1907. The aim of the newly formed organization was to improve cancer research and treatment of cancer and to promote prevention. In recognition of the 100th anniversary of the AACR, this article will examine the role biological research has played in the evolution of cancer surgery.

Four principal aspects with regard to biological research will be addressed: (*a*) whether research played a part in instigating surgical advances that occurred during the 19th and the first half of the 20th centuries; (*b*) whether research formed the basis for the concepts advocated by William S. Halsted, which governed the practice of surgery for the first three quarters of the 20th century; (*c*) a description of findings from my biological research, which I began in 1957, and which was instrumental in replacing Halstedian principles with the guidelines that have been largely responsible for advancing surgical practice to its present status; and (*d*) a consideration of the way in which biological research is currently being subsumed by the technological advances that have initiated a new era in cancer surgery.

Major Advances in Cancer Surgery (19th and 20th Centuries)

The history of cancer surgery has usually been presented chronologically in a series of timelines that catalogue certain "landmark" events during the 19th and 20th centuries (1–6). This article in the AACR Centennial series also includes such a timeline, with both the advances in surgery and the nonsurgical events that contributed to making performance of radical surgery more feasible (Fig. 1).

To gain a better perspective on surgical advances made in the treatment of tumors that arose at a particular site, however, surgical events from timelines are also listed according to the site of tumor origin and the principal surgeon responsible for the advance (Table 1). In addition, I reviewed articles written by the individuals who "fathered" the landmark events and examined numerous articles written by others about those achievements, with the aim of discovering what part, if any, biological research (science) might have played.

Surgical Advances by Tumor Site

Lung. Surgeons who altered the treatment of lung cancer by performing lobectomy, pneumonectomy, or segmental resection of the lung received considerable recognition. Hugh Davies performed the first lobectomy in 1912 using anatomic dissection (7, 8). In reporting the results of Davies' operation, Naef wrote, "If his patient had not died 28 days after the operation, he would have preceded Evarts Graham's first lung resection by 21 years" (8). Although Davies also received acclaim for being "... the earliest advocate of

Note: B. Fisher is a Distinguished Service Professor at the University of Pittsburgh.

This article is dedicated to Edwin R. Fisher, M.D., an experimental pathologist, who died on March 13, 2008. His laboratory and clinical research during the past 50 years played a significant role in the evolution of cancer surgery.

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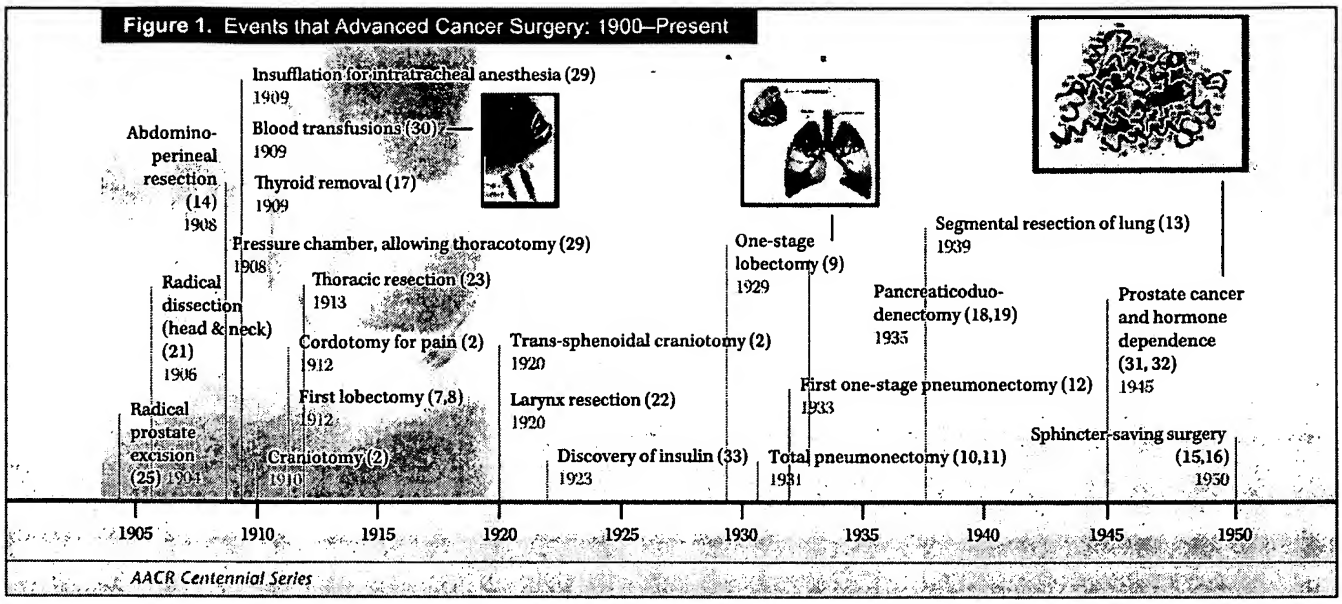

Figure 1. Timeline of advances in surgery.

interdisciplinary teamwork in thoracic medicine" (8), his publication provides no information related to lung cancer other than a technical description of how he performed the operation. A report by Harold Brunn of a single cancer patient who had a one-stage lobectomy provides information only about an operative technique he used (9).

Although Rudolph Nissen was credited with performing the first total pneumonectomy in 1931 (10), he was recognized for an operation that involved the first stage of a pneumonectomy on a 12-year-old girl who developed a lung abscess following trauma (11). It is interesting to note that it was Nissen himself who best described the status of pneumonectomy when he stated, "... the pneumonectomy operation... was far from exhibiting a work of fine or polished technique, and, if merit was attached, it rested on the daring nature of the procedure, and requisite courage reflected more credit upon the patient than the physician" (11). The report of Evarts Graham (12), who was noted for the successful performance of the first one-stage pneumonectomy for lung cancer, was limited entirely to a single case anecdote that described both the technical procedure and the patient's medical history. Strangely enough, no reference to cancer or its treatment appeared in a 1939 report by Edward Churchill and Ronald Belsey of a segmental resection of the lung. Their report described only the technical aspects of that procedure and indicated only that, "... the bronchopulmonary segment may replace the lobe as the surgical unit of the lung " (13).

Rectum. In 1908, W. Ernest Miles performed an abdominoperineal resection to remove a cancer of the rectum (14). At that time, he indicated that the reason techniques used for removal of rectal cancers failed was because they did not completely eradicate the upward spread of cancer from the rectum. He stated, "... removal [of the zone of the upward spread] is just as imperative as is the thorough clearance of the axilla in cases of cancer of the breast if freedom from recurrence is to be hoped for" (14). Not until the 1950s did Harry Bacon begin to alter Miles's operation when he advocated the use of an anal sphincter-preserving procedure (15). Bacon was permitted to conduct his procedure only because of the development of certain technical advances—that is, the successful introduction of anterior resection and end-to-end anastomoses, the introduction of the pull-through excision for cancers of the middle part of the rectum, and the use of a stapling device (16).

Thyroid. Theodore Kocher was the first surgeon to receive the Nobel Prize for his "... work on the physiology, pathology and surgery of the thyroid gland." In fact, his efforts actually related to the surgical treatment of goiter, not cancer of the thyroid (17). In an evaluation of Kocher's contribution to thyroid surgery, it has been noted that, despite his meticulous surgical technique, problems did occur. Kocher himself stated, "In technical terms we have certainly learned to master the operation for goiter... But something else has happened... Removal of the thyroid gland has deprived my patients of what gives them human value. I have doomed people with goitre, otherwise healthy, to a vegetable existence. Many of them I have turned to cretins, saved for a life not worth living ..." Kocher was devastated by these findings and wrote a candid report in 1883 urging surgeons not to perform "total strumectomy [thyroidectomy]" (17).

Pancreas. In 1935, Allen Whipple published information from three patients who had been subjected to a two-stage radical pancreaticoduodenectomy. One patient died postoperatively, one died at 8 months from cholangitis, and a third survived 28 months before dying of liver metastases (18). In 1945, Whipple described the first case of a one-stage procedure for removal of a tumor of the pancreatic islet cells (19). Over the years, he made numerous anatomic modifications to this operation, and, although it represented a technical feat, there is no evidence that it was supported by any findings from biological research. Whipple's operation continued to be modified and is currently being performed to remove acinar and islet cell tumors of the pancreas.

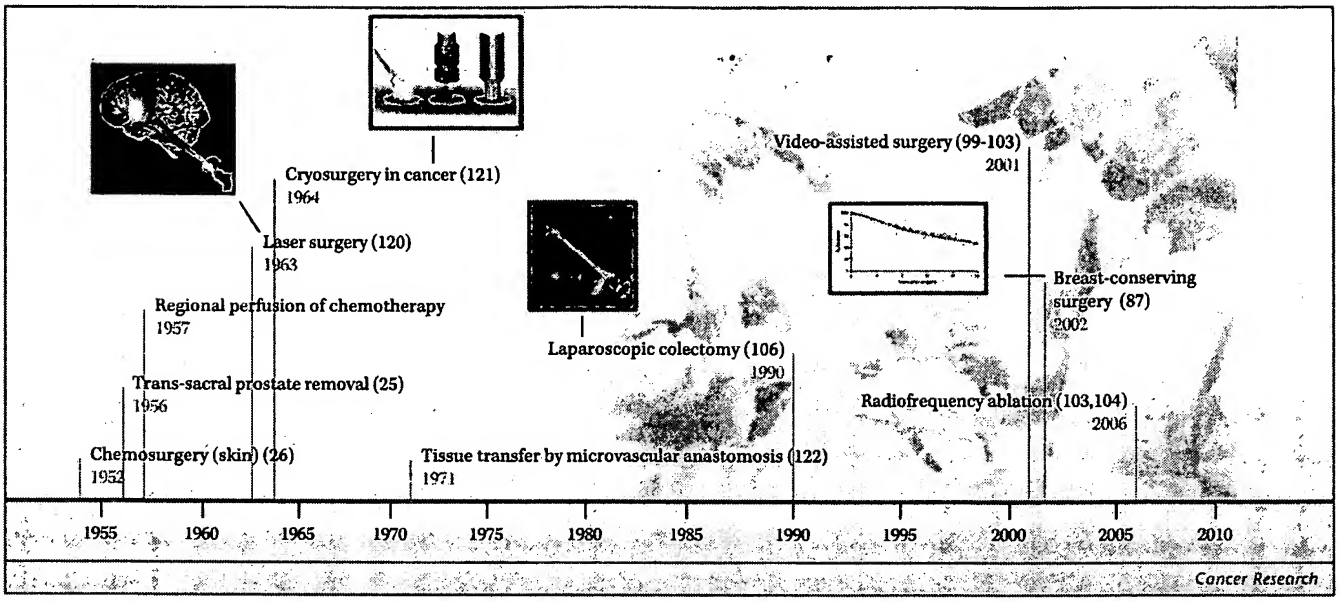

Figure 1 *Continued.*

Head and neck. In 1987 Bobby R. Alford wrote, "The success of the modern head and neck oncologic surgeon in curing patients with head and neck cancer 'exclusive of the thyroid gland' is due in large part to the principles that evolved from the astute clinical observations of George W. Crile" (20), which were published in 1906. Crile, who later founded the Cleveland Clinic, was one of the four surgeons who established the AACR in 1907 and one of a very few who clearly outlined the concepts that led him to perform radical head and neck operations for cancer. Crile used a radical surgical treatment that incorporated "a block dissection of the regional lymphatics as well as the primary focus [and that] was predicated on exactly the same lines as the Halsted operation for cancer of the breast" (21). Thus, it is highly likely that Halsted's principles dictated the efforts of Crile, just as they had governed the work of Miles and other surgeons.

Larynx. The British surgeon Wilfred Trotter pioneered an operation for resection of tumors of the oropharynx, an account of which he published in 1920. Trotter insisted on excision of tumors "regardless of anatomic boundaries" (22), a procedure that was, perhaps, based on Halsted's concepts. Because there were no antibiotics available at the time, "he [Trotter] advocated extraction of all teeth before operation, and relied on elective tracheostomy to secure the airway and reduce infection" (22).

Esophagus. On March 14, 1913, Franz Torek performed the first successful transthoracic resection of a squamous cell carcinoma in the thoracic portion of the esophagus. Howard Lilienthal, who performed the first extrapleural esophagectomy in 1921, noted that neither Torek nor any other surgeon was able to save any patient by the transthoracic approach. As gleaned from available information, Torek's operation, which he performed in 2 hours, 27 minutes, was a feat of both skill and daring (23). It is interesting to note that, at the end of the operation, the patient was given an enema containing hot coffee, whiskey, and strychnine!

Uterus. Although numerous gynecologists performed abdominal hysterectomies at the end of the 19th century, foremost among them was Ernst Wertheim, a Viennese surgeon, whose efforts, in about 1906, gave rise to what was known as the Wertheim operation. Wertheim's landmark accomplishment was the radical hysterectomy, which was based on his premise that, "one had to strive to remove as much as possible the surrounding tissue together with the primary tumor to achieve better results, as is the case with operative procedures for cancer of other organs" (24). It seems highly likely that Halsted's views about breast cancer might have influenced Wertheim's thinking. Regarding the regional lymphatics, however, Wertheim questioned that view by stating that, "In opposition to the view that removal of the entire lymphatic system is the foremost requirement is the fact that it is neither possible nor necessary. Even if one admits that in a few cases carcinomatous metastases may be found in nodes slightly enlarged... carcinoma is never found in spindle-shaped nodes normally present in the pelvis" (24).

Prostate. In 1904, Hugh Young, who had assisted William Halsted with his operations for cancer of the breast at Johns Hopkins University, was, in turn, assisted by Halsted when he performed the first radical suprapubic prostatectomy. It has been suggested that, "Dr. Halsted's new aggressive and radical operations, such as mastectomy with lymph node dissection en bloc, probably stimulated Young to apply similar concepts when he developed his own urologic operations later on" (25).

Skin. The contribution of Frederick Mohs to the treatment of basal cell carcinoma has often been noted as a landmark event on various timelines. In brief, the Mohs micrographic surgical procedure is strictly a technical process and has no relationship to the biology of the type of skin tumors that are being removed (26). It is currently being used to guarantee that the margins of resection are free of tumor and that surgeons remove only as much tissue as is needed.

Lack of biological rationale. As a consequence of my investigation of the events that were considered to be turning points in the evolution of cancer surgery during the 19th and the

Table 1. Advances in cancer surgery according to tumor site

Breast		
1890	Radical mastectomy	W. Halsted
Esophagus		
1880	Esophagectomy	A. Billroth
1913	Thoracic resection	F. Torek
Gynecologic		
1809	Oophorectomy	E. McDowell
1898	Radical hysterectomy	E. Wertheim
Head and neck		
1906	Radical dissection	G. Crile
Larynx		
1873	Laryngectomy	A. Billroth
1920	Resection	W. Trotter
Lung		
1912	First lobectomy	H. M. Davies
1929	One-stage lobectomy	H. Brunn
1931	Total pneumonectomy	R. Nissen
1933	First one-stage pneumonectomy	E. Graham
1939	Segmental resection	E. Churchill
Nervous system		
1910	Craniotomy	H. Cushing
1912	Cordotomy for pain	E. Martin
1920s	Trans-sphenoidal craniotomy	H. Cushing
Pancreas		
1935	Pancreaticoduodenectomy	A. Whipple
Prostate		
1904	Radical excision	H. Young
1956	Trans-sacral removal	B. Vallett
Rectum		
1878	Resection	R. von Volkman
1908	Abdominoperineal resection	W. Miles
1950s	Sphincter-saving Operation	T. Bacon
Skin		
1952	Chemosurgery	F. Mohs
Stomach		
1881	First gastrectomy	A. Billroth
Thyroid		
1909	Thyroidectomy (for goiter)	T. Kocher

first half of the 20th centuries, I concluded that, aside from the desire to eradicate more tumor, there was no biological rationale for the radical surgery that was being performed. My view is in accord with that of Lawrence and Lopez (27), who have stated that, "With few exceptions, all of the surgeons who performed [landmark] operations focused only on the feasibility of removing the part of the anatomic structure containing the cancer" (27). Lawrence and Lopez also noted that, "all of those procedures were established on the basis of either 'armchair' logic or limited clinicopathologic studies" (27) and were "purely empirical" (27), that is, were unrelated to knowledge obtained from experimentation. Thus, it is evident that laboratory and clinical research played little or no role in instigating most of the landmark events in cancer surgery before the second half of the 20th century.

Nonsurgical Advances That Enhanced Radical Surgery

Anesthesia and asepsis. Some uncertainty exists with regard to who discovered ether anesthesia, as well as to when it was first used. George Hill noted in a commentary (1) that John Warren of Boston used ether during an operation that he performed on October 16, 1849. Hill also states, however, that the surgical procedure was performed in 1846, and that Crawford Long used anesthesia during an operation on March 10, 1842. Robert Liston was noted by Hill to have performed a *major* operation under anesthesia on December 21, 1846. Regardless of who was first to use anesthesia, subsequent developments in its use made it feasible for radical cancer surgery to be performed. Sepsis, however, continued to be a major problem. Not until Joseph Lister applied the concepts of Louis Pasteur to surgery by introducing bactericidal therapy with carbolic acid in 1867 and described the principles of antisepsis was it possible to obtain "success" with the ever increasingly radical surgery that had evolved (28).

Prevention of pneumothorax. The greatest advance in thoracic surgery was probably the development of the pressure-differential chamber, which was not an operation but a device for preventing collapse of the lungs due to the entry of air into the thorax during surgery for a thoracotomy. Invented by Ferdinand Sauerbruch in 1908 (29), this instrument was supplanted shortly thereafter by the efforts of Samuel Meltzer, who introduced the use of insufflation for intratracheal anesthesia to more efficiently accomplish inflation of the lungs during entry into the pleural cavity. There is no evidence to indicate that either of these developments was instigated specifically for lung cancer surgery.

Blood transfusion. It is unlikely that the era of radical cancer surgery would have taken place without the efforts of Karl Landsteiner, who was awarded a Nobel Prize in 1930 for his discovery of blood types and his advocacy of the use of blood transfusions. Landsteiner received his award 23 years after Reuben Ottenberg performed the first "modern" blood transfusion at the New York Mt. Sinai Hospital, using the testing of blood type, thus making radical cancer surgery more feasible by decreasing the likelihood of postsurgical mortality (30).

Cancer and hormone dependence. The landmark event that illustrates the strongest relation between surgery and science during the middle of the 20th century was fathered, in about 1941, by Charles Huggins, a University of Chicago surgeon and a 1966 Nobel Laureate (31). Huggins's laboratory and clinical research showed that prostate cancer could be dramatically affected either by castration or by the administration of estrogens, both of which reduced the level of acid phosphatase in the blood. Huggins also showed that it was the synthetic estrogen diethylstilbesterol that caused regression of disseminated prostatic cancer, and in so doing, he initiated the era of cancer chemotherapy (32). He also described the activation of prostatic cancer by androgens and its inhibition by the antiandrogenic effects of orchiectomy and estrogens. The antiandrogenic therapy that Huggins proposed was proved effective and was later adopted throughout the world. Huggins's principle of the hormone dependence of tumors has been applied to other human tumors as well. Although his contributions related to the biology of prostate cancer rather than to the surgical treatment of that tumor, they resulted in the improvement of the surgical treatment of prostate and other cancers by functioning as systemic surgical adjuvant therapy.

As a result of his discovery of insulin, the Canadian surgeon and Nobelist (1923) Frederick Banting similarly made possible radical surgery for cancer of the pancreas—that is, total removal of the

gland that contained insulin-producing cells. Unfortunately, such radical surgery took place without the availability of insulin, and patients subsequently developed uncontrolled hyperglycemia (diabetes; ref. 33).

In 1896, George Beatson (34) made a highly important discovery when he found that removal of the ovaries caused regression of cancer of the breast in women. Beatson's work is classic and is especially noteworthy because it was done before the secretion of endocrine glands had been discovered. Soon it was found that many, but not all, women with mammary cancer benefited from oophorectomy. However, the use of Beatson's procedure subsequently declined and was rarely used as a treatment in cancer of the breast. Huggins, in explaining the reason for that circumstance stated, "The virtual disappearance of a highly useful treatment of disseminated cancer can be attributed in large measure to the empirical nature of the discovery" (35).

The nonsurgical events noted above made it possible for surgeons to perform such "super" radical procedures as extended radical mastectomy, radical head and neck surgery, hemipelvectomy, forequarter and hindquarter amputation, partial evisceration, and even hemicorporectomy (Fig. 2; refs. 36–39). It was apparent, however, that merely having a knowledge of anatomy and being technically facile, as well as courageous, was not sufficient to advance the frontier of surgery.

The Halsted Era (1894 to ca. 1980)

At the same time that the previously described landmark surgical events were occurring, several experimentalists, through efforts that never achieved landmark status, began to introduce "scientific thought" into the process of cancer surgery. When it was realized that a cancer was not a "foreign body" that could be excised locally, but rather, a tumor that could spread, those investigators became interested in the phenomenon of tumor "metastasis," a term first used by Claude Recamier in 1822 to describe secondary growths that had occurred in the brain of a woman with mammary cancer (40).

Rudolf Virchow, the founder of cellular pathology, who formulated the axiom that "all cells come from cells," was perplexed about how tumor cells could possibly traverse one organ, such as the lung, and appear in another, for example, the liver. Virchow proposed the idea of a humoral factor to explain that phenomenon. In 1860, he declared that cancer did *not* spread by the dissemination of tumor cells but, instead, by the elaboration of a parenchymatous juice that passed through the circulation of some organs and affected others (41). Virchow maintained that it was that juice from the primary tumor that transformed connective tissue cells at a secondary site into metastases (42). Despite T.R. Ashworth's first report of the existence of blood-borne tumor cells in 1869 (43), and despite reports by Karl Thiersch (1865; ref. 44) and

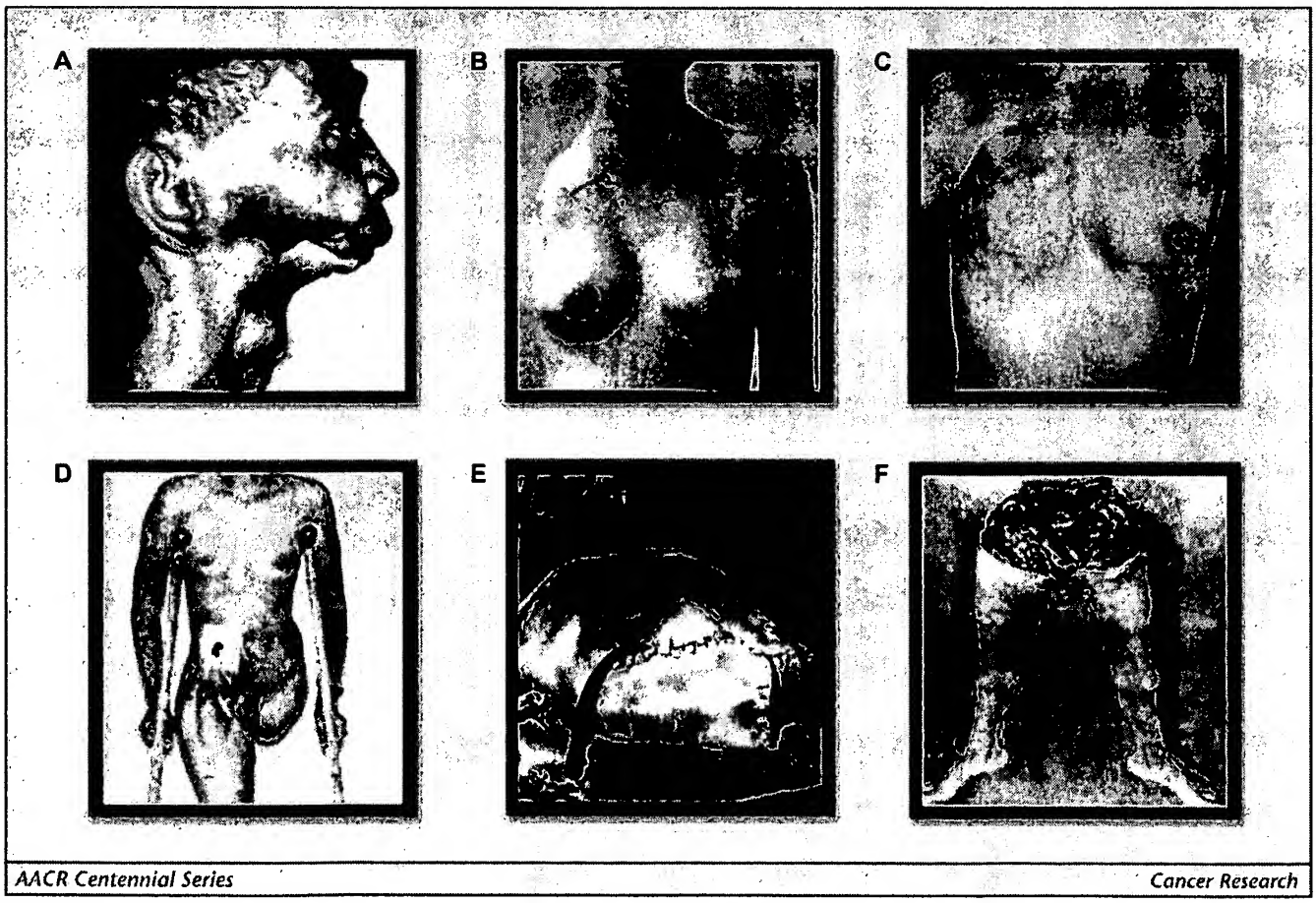

Figure 2. Super-radical surgery. *A*, head and neck; *B*, forequarter amputation; *C*, radical mastectomy; *D*, hemipelvectomy; *E* and *F*, hemi-corporectomy.

Wilhelm Waldeyer (1872; ref. 45), who "established" that metastases occurred via cellular emboli, Virchow, throughout his life, contended that "... perhaps the last word in this question of the clinical nature of metastases was not yet said" (46).

In 1863, Virchow formulated another theory, which held that lymph nodes effectively trapped particulate matter in the lymph (47), and which led to the widely held belief that lymph nodes could provide an effective barrier to the passage of tumor cells. It is remarkable that Virchow was able to reach that conclusion without ever using tumor cells to test the integrity of the lymph node relative to the transmigration of such cells.

Another investigator who made a mark on medical history in the 19th century was Sir James Paget, who introduced the concept of "skip metastases." In Paget's view, lymphatic metastases in breast cancer appeared in distant rather than in proximal axillary lymph nodes as a result of lymphatic communications and the dynamics of lymph flow (48). Because he was skeptical about the purely mechanical explanation for the predilection of certain organs and tissues for developing metastases, Paget proposed, in 1889, that certain organs, such as the liver, possessed a favorable "soil" for such growth, whereas others, such as the spleen, the thyroid, and skeletal muscle, did not. As a result of Paget's concept, two theories for the origin of the metastatic process ultimately arose: One view held that anatomic or mechanical factors were responsible for that process; the other favored the picturesquely labeled "seed-soil" theory of metastasis (49).

The concepts proposed by Virchow and Paget, and by several others with a similar "biological" nature, began to set the stage for a new era of cancer surgery that was to be dominated by William S. Halsted. Over the first three quarters of the 20th century, no one was to be more influential in conditioning the minds of generations of surgeons relative to the management of patients with cancer than was Halsted. His name was associated with the operation referred to as the "radical mastectomy," a procedure that he first described in 1891 and that by 1907, when the meeting to form the AACR was held, was well established as the standard treatment for breast cancer. In an address given at that meeting, on May 8, 1907, Halsted made known his perception of the biology of cancer (Table 2; ref. 50), and consequently, those concepts provided him with the justification for the type of radical surgery he advocated (50).

Table 2. Halstedian concepts of cancer biology (1894)

Tumors spread in an orderly defined manner based on mechanical considerations.
Tumor cells traverse lymphatics to lymph nodes by direct extension, supporting *en bloc* dissection.
The positive lymph node is an indicator of tumor spread and is the instigator of distant disease.
Regional lymph nodes are barriers to the passage of tumor cells.
Regional lymph nodes are of anatomic importance.
The blood stream is of little significance as a route of tumor dissemination.
A tumor is autonomous of its host.
Operable breast cancer is a local-regional disease.
The extent and nuances of operation are the dominant factors influencing patient outcome.

Figure 3. Bernard and Edwin Fisher—1957.

Halsted placed little significance on tumor cells in the bloodstream as a mechanism for the development of metastases, arguing that, "Although it [circulating tumor cells] undoubtedly occurs, I am not sure that I have observed from breast cancer, metastases which seemed definitely to have been conveyed by way of blood vessels." In quoting from W. Sampson Handley (51), he also noted, "In showing that cancer cells in the blood excite thrombosis, and that the thrombosis as it organizes usually destroys or renders them harmless, Goldman and Schmidt seem to have established a fact of primary importance and one which is strongly opposed to the embolic theory as applied to carcinoma." Halsted further emphasized, "We believe with [W. Sampson] Handley that cancer of the breast in spreading centrifugally preserves in the main continuity with the original growth and before involving the viscera may become widely diffused along surface planes."

The surgical approach Halsted recommended was based on his view of the disease and is best revealed by the following statement: "Though the area of disease extend[s], from cranium to knee, breast cancer in the broad sense is a local affection, and there comes to the surgeon an encouragement to greater endeavor with the cognition that the metastases to bone, to pleura, to liver, are probably parts of the whole, and that the involvements are almost invariably by process of lymphatic permeation and not embolic by way of the blood." Halsted stated further, "It must be our endeavor to trace more definitely the routes traveled in the metastases to

bone, particularly to the humerus, for it is even possible in case of involvement of this bone that amputation of the shoulder joint plus a proper removal of the soft parts might eradicate the disease. So, too, it is conceivable that, ultimately, when our knowledge of the lymphatics traversed in cases of femur involvement becomes sufficiently exact, amputation at the hip joint may seem indicated."

As a consequence of the above considerations, Halsted believed that clinically recognizable cancer was a local-regional condition that would be more curable if surgeons were more expansive in their interpretation of what constituted the "region." He also contended that, with the use of better surgical technique using *en bloc* dissection, the "last" cancer cell could be eradicated and, thus, more cancers would be cured. In Halsted's view, it was the inadequate application of surgical skill that was responsible for local-regional tumor recurrences after operation.

History has shown that Halsted's concepts of the biology of breast cancer unfortunately wrongly influenced subsequent generations of surgeons to use surgical procedures that were scientifically unsound. Although his influence waned a bit when, in 1939, Gray reported that the mode of spread of tumor cells to lymph glands was by lymphatic emboli and that such cells did not remain for any length of time within the lumen of lymphatic vessels (52), Halsted's followers dutifully continued to espouse his principles. Moreover, there was little impetus for change because no sufficiently competing ideas arose to challenge Halsted's views. Any challenge that did occur was directed toward questioning whether the radical surgery being performed was sufficiently radical! It has not been possible to determine with certainty what had been accomplished relative to the outcome of patients during the era of radical and super-radical surgery. Systematic record keeping and appropriate data analyses were nonexistent. Technical nuances of surgery, rather than the biological characteristics of a tumor and its host, were deemed responsible for the success or failure of an operation.

Finally, one of the statements that I made in 1970 (53) with regard to Halstedian principles deserves repetition. "It seems obvious that the surgical principles laid down by Halsted were properly conceived and in keeping with his concept of tumor spread. As Richard S. Handley (54) has written, "To belittle Halsted is to commit the stupidity of judging a man's achievement out of context of his time and his circumstances." On the other hand, to continue to endorse uncritically a procedure founded on the principles just described is irrational. If, since Halsted's time, as a result of accumulation of new information relative to this phenomenon—and it cannot be denied that this has occurred—new concepts have arisen, then, either the original surgical principles have become anachronistic or, if they are still valid, they were conceived originally for the wrong reasons" (53).

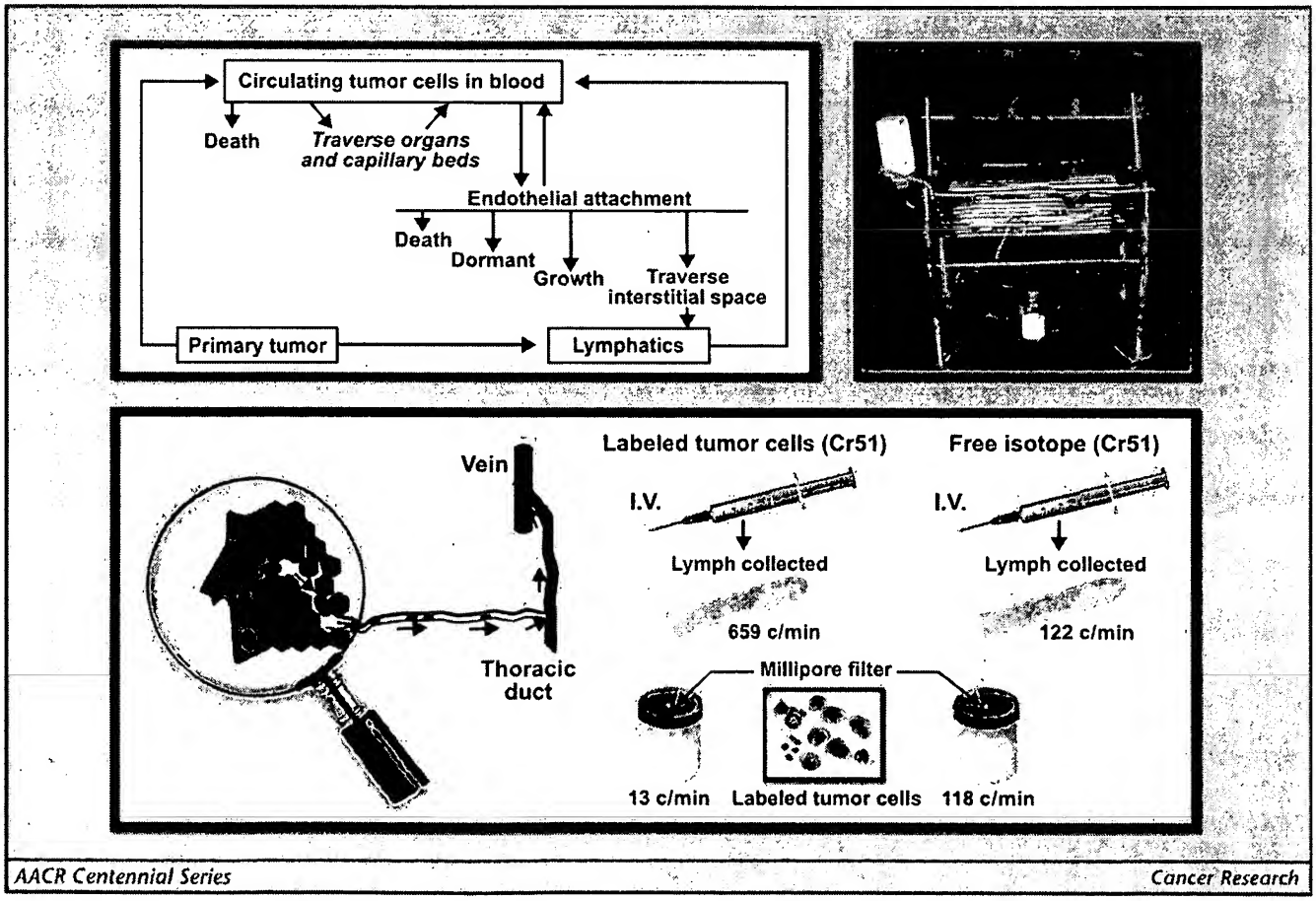

Figure 4. Interrelationship of hematogenous and lymphatic tumor cell dissemination—1966.

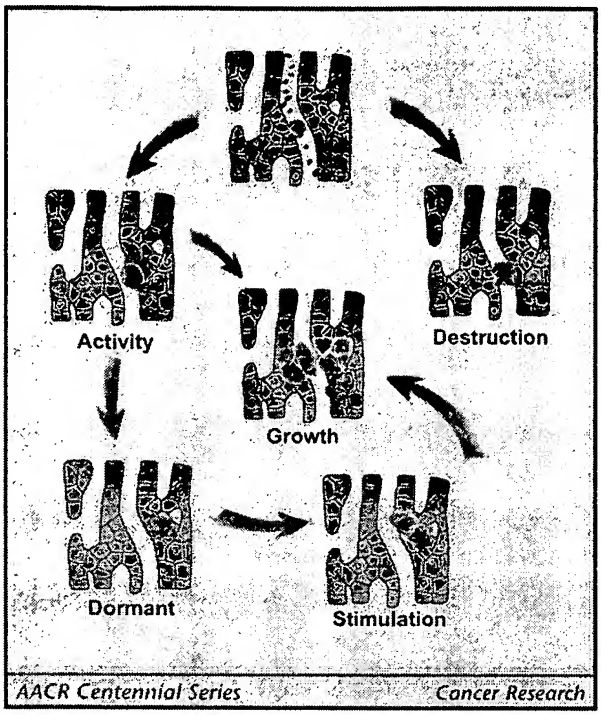

Figure 5. Experimental evidence of the dormant tumor cell—1959.

Biological Research Influences in Cancer Surgery (1980–present)

Beginning of laboratory and clinical research (1957). In 1957, in association with my brother, Edwin R. Fisher, an experimental pathologist, I began laboratory investigations into the biology of tumor metastasis (Fig. 3). Our laboratory and clinical studies, which continued for more than two decades, ultimately led to the creation of a new hypothesis for cancer management. After that hypothesis was tested by means of randomized clinical trials, there resulted, for the first time, a *scientific* basis for the surgical treatment of cancer. (For more information about our studies and their findings, the reader is referred to a series of reports summarized in the next section of this article; refs. 53, 55–65).

When we initiated our laboratory research, the prevailing concept of metastasis was that lymph-borne tumor cells had one destination: the lymph nodes; that tumor cells in the blood vascular system would lodge in the first capillary bed they encountered; and that there was an orderly pattern of tumor spread based on temporal and mechanical considerations. Our experimental findings, however, indicated otherwise. They showed that the blood and lymphatic vascular systems were so interrelated that it was not practical to consider them as independent routes of tumor cell dissemination (Fig. 4; ref. 66). Moreover, we showed via the use of labeled tumor cells that most cells that gained access to an organ via the bloodstream traversed that organ (67). Those findings led us to conclude that, contrary to Halstedian principles, there was *no* orderly pattern to tumor spread and that the phenomenon was not entirely dictated by anatomic considerations but, rather, by intrinsic factors in tumor cells and by a multiplicity of host factors including those in the organs to which tumor cells gained access.

Contrary to the proposals espoused by Virchow and Halsted that regional lymph nodes were effective barriers to tumor cell dissemination, we noted, in another series of investigations, that tumor cells *traversed* lymph nodes, gaining access to efferent lymph, and that they also gained access to the blood vascular system via lymphatic-venous communications within nodes (68–70). Between 1971 and 1977, our experiments showed that regional lymph nodes were capable of destroying tumor cells and that they likely played a role in the initiation (71) and maintenance of tumor immunity (72). As a result of our findings (73), we proposed that regional lymph nodes might be negative for tumor because of those circumstances and not merely because of removal of a tumor before its dissemination.

Investigations that we carried out using regional lymph nodes from women who had undergone radical mastectomy further suggested that regional lymph nodes had biological significance (74). Cells from those nodes expressed immunologic capabilities despite the presence of a growing tumor (73). In addition, we noted that nodes varied with regard to that property both between patients and with the location of nodes in the axilla (75). We subsequently showed that cells from nodes were instigators of a cascade of events that gave rise to cytotoxic effector cells of both the lymphoid and myeloid series (76). Thus, our investigations led us to conclude that biological rather than anatomic factors might be responsible for the appearance of metastasis in certain nodes and the lack of metastasis in others. As a result of those observations, it was my contention that to continue to view lymph nodes as "mechanical receptacles" for trapping tumor cells was an anachronism. Our findings led to the consideration that although more patients with tumor-bearing lymph nodes developed metastases, that did not necessarily mean that the tumor cells in those nodes were instigators of the metastases. Rather, I speculated that the host and tumor factors that permitted tumor growth in nodes might also be responsible for tumor growth at other sites.

In another series of investigations, we were the first to show the reality of dormant tumor cells (Fig. 5; ref. 77) and showed that perturbation of the host by a variety of means could produce lethal metastases from those cells (78). We suggested that "cancer cells alive to begin with may be enduringly capable of growth if

Table 3. The Fisher (alternative) hypothesis of tumor biology (1968)

There is no orderly pattern of tumor cell dissemination.
Tumor cells traverse lymphatics by embolization, challenging the merit of *en bloc* dissection.
The positive lymph nodes are an indicator of a host-tumor relationship that permits development of metastases, rather than the instigator of distant disease.
Regional lymph nodes are ineffective as barriers to tumor cell spread.
Regional lymph nodes are of biological importance.
The blood stream is of considerable importance in tumor dissemination.
Complex host-tumor interrelationships affect every facet of the disease.
Operable breast cancer is a systemic disease.
Variations in local-regional therapy are unlikely to substantially affect survival.

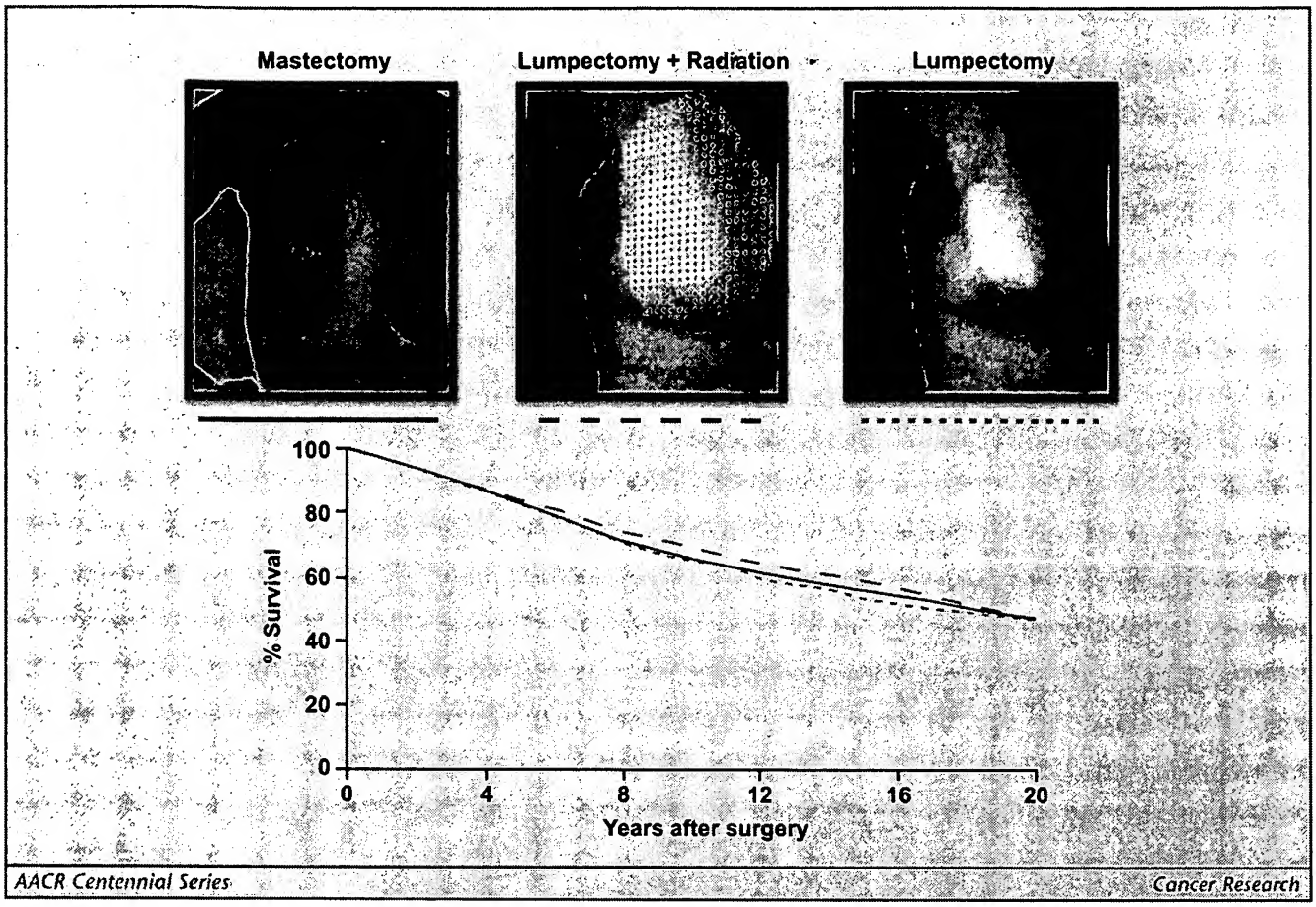

Figure 6. Support for the alternative hypothesis: survival outcome similar for mastectomy, lumpectomy and radiation, or lumpectomy alone.

conditions are favorable." We also considered that local recurrences following operation were not the result of inadequate surgical technique, as Halsted had believed, but, rather, could be due to systemically disseminated cells lodging and growing at a trauma site (79).

The experimental studies we conducted over a period of 15 years showed that a tumor and its metastases were not autonomous of the host but were, instead, related to a variety of host factors, such as blood flow alterations, trauma, biological changes, diet, reticuloendothelial activity, endocrine interrelationships, and others (55, 80). We concluded that because many of the host factors we investigated exhibited opposing effects on the growth of metastases, the possible combinations and permutations that might occur could be responsible for the difficulty in defining host-tumor relationships.

A series of clinical trials we conducted concurrently with our laboratory studies, and which I considered to be an extension of my work in the laboratory, provided new information that raised questions about the concepts on which treatment for breast cancer, as well as other cancers, was based. Recurrence and survival were found to be independent of the number of axillary nodes removed (81) and examined. Tumor location also failed to influence prognosis (82), as was observed in patients who had radical mastectomies without removal of internal mammary nodes in the mediastinum. In those women, a similar rate of treatment failure and survival occurred regardless of whether the tumors were located in the inner or outer half of the breast.

During the late 1960s, tumor size also began to be viewed as a marker of breast cancer heterogeneity. Neoplastic surgery was based on the concept that the time of a tumor's existence, as measured by size, determined surgical success (83) and that the earlier the operation (thus, the smaller the tumor), the better the chance for a cure. In an effort to determine the validity of that concept, we obtained information that led us to conclude that size did not necessarily relate to either "earliness" or "lateness" of a tumor and that outcome was related to tumor and/or host factors (53).

Formulation and testing of the Fisher alternative hypothesis (ca. 1968). From a historical perspective, it is interesting to note that in 1865 the French physiologist Claude Bernard, who is considered to be the father of experimental medicine, had introduced his "scientific process" (84) and promulgated the thesis that, "A hypothesis is... the obligatory starting point for all experimental reasoning." According to Bernard, a hypothesis was of value only if it could be tested. Others had noted that a hypothesis constructed without an adequate program for estimating its worth "is a burden to science and to the world" and emphasized that any scientist who put forth hypotheses that could not be tested

"is a purveyor of rubbish" (85). There is no evidence to indicate that Halsted had formulated a hypothesis. Halstedian principles had their origins in anecdotalism, and their validity was accepted without being tested.

In the late 1960s, it became apparent that the results from our laboratory and clinical studies all had the same characteristic: They did not conform to Halstedian principles. Instead, our findings provided the basis for the formulation of a hypothesis that was biological in concept (Table 3). Its components were completely antithetical to those that had dictated Halstedian surgery (60). On the basis of Bernard's thesis, I realized that the validity of my hypothesis needed to be tested because only with scientific confirmation would it be permissible for a new generation of surgeons to abandon the surgical heritage that had been passed on to them by William Halsted.

The opportunity to evaluate the tenets of my hypothesis occurred in 1971, when I initiated a randomized clinical trial involving almost 2,000 women. The aim of that trial was to test the hypothesis by comparing the outcomes of those women in three treatment groups. One group was treated with a Halsted radical mastectomy; two other groups received less extensive operations. One of the latter two groups also received postoperative breast irradiation. Despite the differences in treatment, during 25 years of follow-up, the outcomes of the groups were not significantly different (86). Those findings supported the hypothesis by corroborating my previous contention that variations in local-regional treatment were unlikely to substantially affect survival and, most important, eliminated any considerations that might have contradicted evaluating breast-conserving operations by means of a second randomized trial. In 1976, I initiated another trial to reevaluate the alternative hypothesis and, at the same time, determine whether breast-conserving surgery—lumpectomy—was as effective as breast removal. In that study, nearly 2,000 women were randomly distributed among three treatment groups: One group underwent mastectomy, a second received lumpectomy alone, and a third received lumpectomy followed by breast irradiation. Findings through 20 years of follow-up showed no significant difference in the outcome of the three groups (Fig. 6; ref. 87). Those findings yielded additional support for my hypothesis and provided further confirmation that there was neither a biological nor a clinical rationale for opposition to breast-conserving surgery.

As a result of the alternative hypothesis and its validation by appropriately designed randomized clinical trials that produced data that were subjected to rigorous biostatistical analysis, after three quarters of a century (1975), Halstedian concepts and the expansive operations fostered by them reached their zenith and gradually began to be relegated to the dustbin of history. Those concepts, which had resulted in the mutilating radical and super-radical surgical procedures that had been used for treating not only breast cancer but also melanoma, colorectal cancer, soft tissue sarcoma, thyroid and other head and neck cancers, and lung cancer, could now be viewed merely as markers against which progress in the understanding and treatment of cancer could be measured.

As a consequence of the tenets of the alternative hypothesis, it became apparent that only with the use of systemic therapy could improved survival after surgery be achieved, and that further manipulation of local-regional treatment by means of surgery and/or radiation therapy, another modality governed by Halstedian principles, was likely to be futile. Fortunately, at the same time that the rationale for the surgical treatment of cancer was being redefined, the era of systemic adjuvant therapy was beginning to evolve. That circumstance was also to have a profound effect on the role of surgery for the treatment of cancer.

Advent of systemic therapy as an adjunct to surgery (1972). Although, in the mid-1950s, it had been observed in experimental animals that chemotherapy had a cytotoxic effect on tumor cells in the blood (88), it was not until the early 1970s that I initiated the first trial to evaluate the use of postoperative chemotherapy for the treatment of cancer. Kinetic principles of tumor growth elucidated from animal studies conducted during the 1960s and early 1970s had resulted in the formulation of a hypothesis that could be tested in clinical trials (89). The initial results of that study, which were reported in 1975, showed that such therapy could alter the natural history of patients with primary breast cancer (90). A series of studies in which antiestrogens (tamoxifen) were used postoperatively, either alone or in combination with or without chemotherapeutic agents, firmly established the worth of such therapy (91–95). The treatment of patients who had no identifiable metastatic disease with systemic adjuvant therapy because of the possibility that in the future they might develop distant disease was a revolutionary departure from previous strategies.

As a result of those findings, I concluded, in 1980, that two independent paradigms governed the management of cancer. The first was related to the use of surgery to eradicate local and regional disease; the second was related to the eradication of systemic disease. When it was discovered that systemic adjuvant therapy—that is, chemotherapy and/or tamoxifen—decreased local and regional recurrence as well as distant disease after minimal surgery, there was reason to conclude that the two independent paradigms had converged into one unified paradigm. It was no longer possible to consider the surgical management of breast cancer as an independent therapeutic strategy, and as a

Table 4. Current technology used in cancer surgery

Laser (light amplification by stimulated emission of radiation) surgery
Cryosurgery
Electrosurgery
Endoscopic surgery
Laparoscope
Thoracoscope
Mediastinoscope
High-intensity focused ultrasound
Microwaves
Radiowaves (radiofrequency cytoablation)
Stereotactic radiation (from cobalt-60 source)
Gamma Knife
CyberKnife
Magnetic resonance imaging
Robotic surgery
Smart scalpel
AESOP (Automated Endoscopic System for Optimal Position)
Da Vinci
Zeus systems
Socrates (surgical collaboration system linking remote surgeons directly with operating rooms)
Hermes (operating room central nervous system)
Navigator
Nanorobots

consequence, there arose the need to determine how other therapeutic strategies and their mode of administration influenced surgical treatment and vice versa. The use of preoperative therapy related to that circumstance.

The hypotheses that I formulated from biological and clinical information obtained during the 1980s led me to initiate the first randomized clinical trial to evaluate the role of preoperative chemotherapy (96, 97). A finding of particular importance in that study was that reduction in the size of a large tumor after preoperative therapy permitted more patients to be treated with breast-conserving surgery (lumpectomy and breast irradiation). Those findings showed that in patients who received preoperative therapy, the outcome with regard to disease-free survival and survival was the same as when that therapy was given after mastectomy. The advent of the use of systemic therapy resulted in further reducing the role of surgery in cancer treatment to the extent that, today, surgery might be considered to be the adjuvant therapy.

The Technological Era of Surgery (2000–present)

As surgeons began to be free from the constraints imposed on them by Halstedian concepts, radical cancer surgery began to be replaced by less extensive operations. The use of regional and systemic surgical adjuvant therapy in the form of radiation, chemotherapy, and/or hormonal therapy and the ability to diagnose progressively smaller tumors also played a role in further decreasing the need for contemplating the use of radical surgery. While those aspects of the evolution of cancer surgery were occurring, research in engineering was making feasible new technological advances. Those accomplishments opened the door to a new surgical era that is still in its infancy—an era in which the scalpel is no longer the symbol (Table 4). In fact, it is becoming increasingly more difficult to separate what we commonly think of as surgery from other forms of therapy that are evolving for the local-regional treatment of cancer. It has even been predicted that, in the near future, robotic surgery will replace the surgery currently in vogue (98).

Treatment According to Tumor Site

Lung. Since the onset of the 21st century, there has been an increase in the number of publications that describe drastic changes in the management of patients with lung cancer, particularly those with small tumors. Thoracotomy, which previously used long incisions, and which involved cutting muscles and spreading ribs to remove a lobe of the lung, is rapidly being replaced by minimal or noninvasive procedures. The use of video-assisted thoracic surgery has achieved considerable popularity in that regard. A videoscope that is inserted through an intercostal space and then connected to a TV monitor provides guidance for removal of both a lobe of lung and the mediastinal lymph nodes. Comments about the worth of video-assisted thoracic surgery by surgeons who have reported their experience with the procedure are variable (99–103). It was recently stated, "It is more likely that video-assisted thoracic surgery will find a defined, specialized role for a specific patient population rather than being used on every patient, by every surgeon at every hospital" (103).

Other techniques, such as those that use thermal energy, are also being used to remove lung cancers without opening the chest. For example, in patients with small tumors or in those who are at poor risk, radiofrequency ablation is being used (103). When radiation therapy is used in conjunction with radiofrequency ablation, the value of the latter is enhanced (104). Another technical advance, the CyberKnife, which can be used to remove lung cancer, consists of a miniature linear accelerator that is attached to a robotic arm so as to deliver highly concentrated beams of radiation that converge at a single site in the lung—in the tumor itself (105).

Colon and rectum. The first report of the use of laparoscopic (LAP) colectomy for the removal of colon cancer appeared in 1990 (106). In 2004, the results from a large multi-institutional randomized trial, after 4 years of follow-up, concluded that, "the rates of recurrent cancer were similar after laparoscopically assisted colectomy and open colectomy, suggesting that the laparoscopic approach is an acceptable alternative to open surgery for colon cancer" (107). Data reported from other clinical trials confirmed those findings and emphasized the worth of laparoscopic surgery in that patients made a more rapid recovery and had fewer complications as well as a shorter hospital stay (108–111). It was stated that, "Finally LAP colectomy may be a first step toward a newer, less invasive, operative approach, namely Natural Orifice Transluminal Endoscopic Surgery" (110). Whereas it has been stated, "There is no reason not to offer laparoscopic colectomy in all stages of colon cancer in contemporary clinical practice" (112), credible data have not yet become available to advocate its use in rectal cancer resection outside of a clinical trial.

Brain. Technologic advances are drastically altering the surgical treatment of brain tumors. Minimally invasive procedures that remove such tumors without injuring normal tissue are being developed. During the 1980s, neurosurgeons began using the microscope for that purpose. The extent of their vision of the operative site, however, was limited. With the advent of the solid-lens or fiberoptic endoscope that is connected to a high-resolution camera, a xenon light source, a video monitor, and compatible instrumentation, the surgeon now has a wide-angle view of the operative field that is being traversed. Such a technique has been used for the removal of tumors in the pituitary and for intraventricular tumors (113).

Another technological advance related to the development of robotics and to the use of the "Smart Scalpel" could further change brain surgery as we have known it. The Smart Scalpel has a microlaser attached to it that is capable of precisely detecting and destroying cancer cells during surgery. Because cancer cells contain more protein and, consequently, are denser, the Smart Scalpel avoids damaging cells that are noncancerous. As a result, surgeons can limit their efforts to removing only those cells that have been flagged as cancerous. Another new innovation is the "Gamma Knife," which can eradicate brain tumors by administering a concentrated radiation dose from a cobalt-60 source. Multiple beams of radiation intersect to focus on a targeted area of abnormal brain tissue while adjacent normal tissue is spared.

Breast. The surgical treatment of breast cancer is also being profoundly altered as a consequence of the technological revolution. Whereas radical and super-radical mastectomy have been replaced during the last two decades by the use of breast-conserving surgery, more minimally invasive and noninvasive procedures are currently being evaluated. Endoscopic breast-conserving surgery for tumor and sentinel-node removal has been used to both improve cosmesis and shorten the time of operation (114). Stereotactic removal of small tumors, their ablation by radiofrequency or interstitial laser beams, magnetic resonance

imaging, guided focused ultrasound, and cryosurgery are all undergoing evaluation for the treatment of breast cancer (115, 116).

Other sites. Conventional surgical methods that have been used for the treatment of patients with laryngeal cancer are being replaced by the use of endoscopic laser surgery (117). Similarly, the removal of urologic tumors of the prostate and kidney by means of endoscopic surgery with the Da Vinci robotic system and the Zeus-associated endoscope for pelvic lymph node dissection have attracted attention (98).

This brief description of the ways in which current technological advances are revolutionizing the surgical treatment of cancer is likely to be only the prelude to greater change, for, while the use of endoscopic surgery is gaining acceptance, new tools to overcome deficiencies in it are being considered (118). Computer-based methods for planning, monitoring, and controlling surgical procedures are becoming a reality. An interventional magnetic resonance imaging–guided robot-assisted system and a magnetic resonance imaging–compatible endoscope are considered likely to play an important future role in the conduct of surgery. Similarly, it is anticipated that nanorobots will be able to precisely define and map cancer tissue and, thus, provide the surgeon with precise information about target areas that require dissection (119).

As occurred with the use of radical and super-radical surgery during the Halstedian era, anecdotal reports of the use of these new technologies are abundant. It is evident that quality of life is better following their use. However, there is need for more information obtained from appropriate scientific methodologies, such as clinical trials before it can be known whether freedom from tumor recurrence and survival are the same or better than that being obtained with current surgical treatment. Because these new instruments are used to eliminate localized tumor, and because cancer is a "systemic" disease, the need for that information is imperative.

Comment

For nearly 50 years it has been my contention that progress in the surgical treatment of cancer would occur only from research that resulted in a better comprehension of the biology of the disease. There is little evidence, however, to indicate that today's technological innovations related to surgery have been the product of biological principles. Advances in engineering research and the resulting empiricism have led to the use of these innovations. Thus, before and after the founding of the AACR, the evolution of cancer surgery has been influenced by surgical technique to a greater extent than by knowledge related to the biological nature of the disease. Nonetheless, it has been the results from laboratory and clinical research that have provided justification for opening the door to many of the changes during the past 30 years.

Although current and future technological developments will continue to play a role in the surgical treatment of cancer, it is ultimately the findings from research in molecular biology and genetics that will dictate the future status of cancer treatment and, ultimately, the fate of surgery. By the time the AACR celebrates its sesquicentennial, it is almost a certainty that cancer surgery, as it was performed during the first 100 years of the AACR, will be supplanted by other modalities that have resulted from scientific investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Hill GJ II. Historic milestones in cancer surgery. Semin Oncol 1979;6:409–27.
2. Rosenberg SA. Principles of surgical oncology. In: DeVita VT, Jr., Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 1–11.
3. Sabel MS, Diehl KM, Chang AE. Principles of surgical therapy in oncology. In: Chang AE, Ganz PA, Hayes DF, Kinsella T, Pass HI, Schiller JH, Stone RM, Strecher V, editors. Oncology—an evidence-based approach. New York: Springer; 2005. p. 58–72.
4. Pollock RE, Morton DL. Principles of surgical oncology. In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Jr., Gansler TS, Holland J, Frei E III, editors. Cancer medicine. 7th ed. Hamilton, Ontario (Canada): B.C. Decker; 2006. p. 503–16.
5. Surgical Oncology Clinics of North America. The evolution of radical cancer surgery. Lopez MJ, editor. July 2005. Vol. 14, No. 3. p. 441–653.
6. Olson JS. The History of cancer: an annotated bibliography. New York: Greenwood Press; 1989. p. 296–317.
7. Davies HM. Recent advances in the surgery of the lung and pleura. Br J Surg 1914;1:228–58.
8. Naef AP. Hugh Morriston Davies: first dissection lobectomy in 1912. Ann Thorac Surg 1993;56:988–9.
9. Brunn H. Surgical principles underlying one-stage lobectomy. Arch Surg 1929;18:490–515.
10. Vanderpool D. Bright leaves, dark leaves. J Am Coll Surg 2003;196:313–8.
11. Watson WL. Radical surgery for lung cancer: evolution of the operation of radical pneumonectomy and five-year end results. Cancer 1956;9:1167–72.
12. Graham EA, Singer JJ. Successful removal of an entire lung for carcinoma of the bronchus. J Am Med Assoc 1933;101:1371–4.
13. Churchill ED, Belsey R. Segmental pneumonectomy in bronchiectasis: the ligula of the left upper lobe. Ann Surg 1939;109:481–99.
14. Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. Lancet 1908;2:1812–3.
15. Bacon HE. Abdominoperineal proctosigmoidectomy with sphincter preservation: five-year and ten-year survival after "pull-through" operation for cancer of the rectum. J Am Med Assoc 1956;160:628.
16. Hughes ESR. The Harry Ellicott Bacon oration: the development of a restorative operation for carcinoma of the rectum. Aust N Z J Surg 1981;51:117–9.
17. Ball C. Kocher's mask. Anaesth Intensive Care 1995; 23:535.
18. O'Sullivan A. Whipple pancreaticoduodenectomy: a historical comment. Grand Rounds 2007;7:1–2.
19. Whipple AO. Pancreaticoduodenectomy for islet carcinoma. Ann Surg 1945;121:847–52.
20. Alford BR. Landmark perspective: the heritage of the radical neck dissection. J Am Med Assoc 1987;258:3294–5.
21. Crile G. Excision of cancer of the head and neck, with special reference to the plan of dissection based on one hundred and thirty-two operations. J Am Med Assoc 1906;47:1780–8.
22. George KS, McGurk M. Wilfred Batten Lewis Trotter 1872–1939. Br J Oral Maxillofac Surg 2005;43:500–4.
23. Scannell JG. Franz J.A. Torek (1861–1938). J Thorac Cardiovasc Surg 1997;114:690–1.
24. Speert H. Obstetrical-gynecological eponyms: Ernest Wertheim and his operation for uterine cancer. Cancer 1956;9:859–65.
25. Engel RME. Hugh Hampton Young: father of American urology. J Urol 2003;169:458–64.
26. Mohs FE. Chemosurgery: a microscopically controlled method of cancer excision. Arch Surg 1941;42:279–95.
27. Lawrence W, Jr., Lopez MJ. Radical surgery for cancer: a historical perspective. Surg Oncol Clin N Am 2005;14:441–6.
28. Lister J. The collected papers of Joseph Baron Lister. Oxford (England): Clarendon Press; 1909.
29. Cherian SM, Nicks R, Lord RSA. Ernest Ferdinand Sauerbruch: rise and fall of the pioneer of thoracic surgery. World J Surg 2001;25:1012–20.
30. Bauman R. Karl Landsteiner: blood on his mind. [cited 2008 Apr 16]; Available from: http://www.worldandi.com/subscribers/feature_detail.asp?num=24922.
31. Huggins C. Studies on prostate cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.
32. Classics in oncology. Charles Brenton Huggins (1901-). CA Cancer J Clin 1972;22:230–1.
33. Rosenfeld L. Insulin: discovery and controversy. Clin Chem 2002;48:2270–88.
34. Beatson GT. On the treatment of inoperable cases of

carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet 1896;2:104–7.
35. Huggins CB. The hormone-dependent cancers. Bull N Y Acad Med 1963;39:752–7.
36. Brunschwig A. Hemipelvectomy in combination with partial pelvic exenteration for uncontrolled recurrent and metastatic cancer of the cervix, five-year survival. Surgery 1962;52:299–304.
37. Ferrara BE. Hemicorporectomy: a collective review. J Surg Oncol 1990;45:270–8.
38. Weaver JM, Flynn MB. Hemicorporectomy. J Surg Oncol 2000;73:117–24.
39. Miller TR, Mackenzie AR, Randall HT. Translumbar amputation for advanced cancer: indications and physiologic alterations in four cases. Ann Surg 1966; 164:514–21.
40. Recamier JC. Recherches sur le traitement du cancer par la compression, et sur l'histoire generale de la meme maladie. Paris: 1829. 2V:110.
41. Virchow R. Cellular pathology. Frank Chance, translator. London: Churchill; 1860. p. 459–60.
42. Editorial: Histogenesis of cancer. Lancet 1875;2: 104–5.
43. Ashworth TR. A case of cancer in which cells similar to those in the tumours were seen in the blood after death. Aust Med J 1869;14:146.
44. Thiersch K. Der epithelialkrebs, namentlich der haut. Leipzig: W. Engelmann; 1865.
45. Waldeyer W. Die entwicklung der carcinome. Arch Pathol Anat Physiol Klin Med 1872;55:67–159.
46. Ackerknecht EH. Rudolph Virchow. Madison: The University of Wisconsin Press; 1953. p. 105.
47. Virchow R. Cellular pathology. Frank Chance, translator. Philadelphia: J.B. Lippincott Co.; 1863.
48. Paget S. Lectures on surgical pathology. 3rd ed. London: Longman; 1870. p. 821.
49. Paget S. The distribution of secondary growth in cancer of the breast. Lancet 1889;1:571–3.
50. Halsted WS. The results of radical operations for the cure of carcinoma of the breast. Ann Surg 1907;46: 1–19.
51. Handley WS. Cancer of the breast and its operative treatment. London: John Murray:1906. p. 13.
52. Gray HJ. Relation of the lymphatic vessels to the spread of cancer. Br J Surg 1939;26:462.
53. Fisher B. The surgical dilemma in the primary therapy of invasive breast cancer: a critical appraisal. Curr Probl Surg 1970(Oct):3–53.
54. Handley RS. The technic and results of conservative radical mastectomy (Patey's operation). Prog Clin Cancer 1965;1:462.
55. Fisher B, Fisher ER. The biology of metastasis. In: Davis JH, editor. Current concepts in surgery. New York: McGraw-Hill Book Company, Inc.; 1965. p. 321–51.
56. Fisher B, Fisher ER. Metastases of cancer cells. In: Busch H, editor. Methods in cancer research. Vol. 1. New York: Academic Press; 1967. p. 243–86.
57. Fisher ER, Fisher B. Recent observations on concepts of metastasis. Arch Pathol 1967;83:321–4.
58. Fisher B. The changing role of surgery in the treatment of cancer. In: Becker FF, editor. Cancer: a comprehensive treatise. Vol. 6. New York: Plenum Publishing Corp.; 1977. p. 401–21.
59. Fisher B, Gebhardt MC. The evolution of breast cancer surgery: past, present, and future. Semin Oncol 1978;5:385–94.
60. Fisher B. Laboratory and clinical research in breast cancer—a personal adventure: The David A. Karnofsky Memorial Lecture. Cancer Res 1980;40:3863–74.
61. Fisher B. Cancer surgery: a commentary. Cancer Treat Rep 1984;68:31–41.
62. Fisher B. The role of science in the evolution of breast cancer management. In: Ames FC, Blumenschein GR, Montague ED, editors. Current controversies in breast cancer. Austin (TX): University of Texas Press; 1984. p. 1–21.
63. Fisher B. The interdependence of laboratory and clinical research in the study of metastases. In: Nicolson GL, Milas L, editors. Cancer invasion and metastasis: biologic and therapeutic aspects. New York: Raven Press; 1984. p. 27–46.
64. Fisher B. The revolution in breast cancer surgery: science or anecdotalism? World J Surg 1985;9:655–66.
65. Fisher B. From Halsted to prevention and beyond: advances in the management of breast cancer during the twentieth century. Eur J Cancer 1999;35:1963–73.
66. Fisher B, Fisher ER. The interrelationship of hematogenous and lymphatic tumor cell dissemination. Surg Gynecol Obstet 1966;122:791–8.
67. Fisher B, Fisher ER. The organ distribution of disseminated ^{51}Cr-labeled tumor cells. Cancer Res 1967;27:412–20.
68. Fisher B, Fisher ER. Transmigration of lymph nodes by tumor cells. Science 1966;152:1397–8.
69. Fisher B, Fisher ER. Barrier function of lymph node to tumor cells and erythrocytes: I. Normal nodes. Cancer 1967;20:1907–13.
70. Fisher B, Fisher ER. Barrier function of lymph node to tumor cells and erythrocytes: II. Effect of X-ray, inflammation, sensitization and tumor growth. Cancer 1967;20:1914–9.
71. Fisher B, Fisher ER. Studies concerning the regional lymph node in cancer: I. Initiation of immunity. Cancer 1971;27:1001–4.
72. Fisher B, Fisher ER. Studies concerning the regional lymph node in cancer: II. Maintenance of immunity. Cancer 1972;29:1496–501.
73. Fisher B, Saffer E, Fisher ER. Studies concerning the regional lymph node in cancer: IV. Tumor inhibition by regional lymph node cells. Cancer 1974; 33:631–6.
74. Fisher B, Saffer EA, Fisher ER. Studies concerning the regional lymph node in cancer: III. Response of regional lymph node cells from breast and colon cancer patients to PHA stimulation. Cancer 1972;30: 1202–15.
75. Fisher B, Saffer EA, Fisher ER. Studies concerning the regional lymph node in cancer: VII. Thymidine uptake by cells from nodes of breast cancer patients relative to axillary location and histopathologic discriminants. Cancer 1974;33:271–9.
76. Fisher B, Hanlon JT, Linta J, Saffer E, with the technical assistance of Coyle J, Rudock C. Tumor specificity, serum inhibition, and influence of regional lymph nodes on cytotoxic macrophages from cultured bone marrow. Cancer Res 1977;37:3628–33.
77. Fisher B, Fisher ER. Experimental evidence in support of the dormant tumor cell. Science 1959;130:918–9.
78. Fisher B, Fisher ER. Experimental studies of factors influencing hepatic metastases: III. Effect of surgical trauma with special reference to liver injury. Ann Surg 1959;150:731–44.
79. Fisher B, Fisher ER, Feduska N. Trauma and the localization of tumor cells. Cancer 1967;20:23–30.
80. Fisher ER, Fisher B. Some theoretical and practical considerations of metastases. Contemp Surg 1974;4: 85–9.
81. Fisher B, Slack NH. Number of lymph nodes examined and the prognosis of breast carcinoma. Surg Gynecol Obstet 1970;131:79–88.
82. Fisher B, Slack NH, Ausman RK, Bross IDJ. Location of breast carcinoma and prognosis. Surg Gynecol Obstet 1969;129:705–16.
83. Fisher B, Slack NH, Bross IDJ. Cancer of the breast: size of neoplasm and prognosis. Cancer 1969; 24:1071–80.
84. Bernard C. Introduction à l'étude de la médicine experimentale. Paris: 1865.
85. Root-Bernstein RS. Discovering. Cambridge (MA): Harvard University Press; 1989. p. 501.
86. Fisher B, Jeong J-H, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002;347:567–75.
87. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
88. Shapiro DM, Fugmann RA. A role of chemotherapy as an adjunct to surgery. Cancer Res 1957;17: 1098–101.
89. Skipper HE. Kinetics of mammary tumor cell growth and implications for therapy. Cancer 1971;28: 1479–99.
90. Fisher B, Carbone P, Economou SG, et al. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer: a report of early findings. N Engl J Med 1975;292:117–22.
91. Fisher B, Redmond C, Brown A, et al. Adjuvant chemotherapy with and without tamoxifen in the treatment of primary breast cancer: 5-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. J Clin Oncol 1986;4:459–71.
92. Fisher B, Redmond C, Legault-Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. J Clin Oncol 1990;8:1005–18.
93. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989;320:479–84.
94. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 1996;88: 1529–42.
95. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 1997;89: 1673–82.
96. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997;15:2483–93.
97. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16: 2672–85.
98. Hashizume M, Tsugawa K. Robotic surgery and cancer: the present state, problems and future vision. Jpn J Clin Oncol 2004;34:227–37.
99. Nomori H, Horio H, Naruke T, Suemasu K. What is the advantage of a thoracoscopic lobectomy over a limited thoracotomy procedure for lung cancer surgery? Ann Thorac Surg 2001;72:879–84.
100. Gharagozloo F, Tempesta B, Margolis M, Alexander EP. Video-assisted thoracic surgery lobectomy for stage I lung cancer. Ann Thorac Surg 2003; 76:1009–15.
101. McKenna RJ, Jr., Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. Ann Thorac Surg 2006;81:421–6.
102. Shiraishi T, Shirakusa T, Hiratsuka M, Yamamoto S, Iwasaki A. Video-assisted thoracoscopic surgery lobectomy for c-$T_1N_0M_0$ primary lung cancer: its impact on locoregional control. Ann Thorac Surg 2006;82:1021–6.
103. Sherwood JT, Brock MV. Lung cancer: new surgical approaches. Respirology 2007;12:326–32.
104. Dupuy DE, DiPetrillo T, Gandhi S, et al. Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. Chest 2006;129:738–45.
105. Donington JSSL, Loo B, Wakelee H, Whyte R, Le Q. Single fraction stereotactic radiosurgery (SFSR) for the treatment of stage 1 non-small cell lung cancer (NSCLC). San Diego, CA, 2007.
106. Phillips EH, Franklin M, Carroll BJ, Fallas MJ, Ramos R, Rosenthal D. Laparoscopic colectomy. Ann Surg 1992; 216:703–7.
107. The Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350: 2050–9.
108. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718–26.
109. The Colon cancer Laparoscopic or Open Resection Study Group. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477–84.

110. Nelson H, Boller A-M. The role of clinical trials in the development of novel surgical techniques. J Surg Oncol 2007;96:704–9.
111. Schwenk W, Haase O, Neudecker J, Muller JM. Short-term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2007;20:CD003145.
112. Boller A-M, Nelson H. Colon and rectal cancer: laparoscopic or open? Clin Cancer Res 2007;13(22 suppl):6894s–6s.
113. Badie B, Brooks N, Souweidane MM. Endoscopic and minimally invasive microsurgical approaches for treating brain tumor patients. J Neurooncol 2004;69: 209–19.
114. Lee E-K, Kook S-H, Park Y-L, Bae W-G. Endoscopy-assisted breast-conserving surgery for early breast cancer. World J Surg 2006;30:957–64.
115. Vlastos G, Verkooijen HM. Minimally invasive approaches for diagnosis and treatment of early-stage breast cancer. Oncologist 2007;12:1–10.
116. Singletary SE. Minimally invasive techniques in breast cancer treatment. Semin Surg Oncol 2001;20: 246–50.
117. Genden EM, Ferlito A, Silver CE, et al. Evolution of the management of laryngeal cancer. Oral Oncol 2007; 43:431–9.
118. Hashizume M. MRI-guided laparoscopic and robotic surgery for malignancies. Int J Clin Oncol 2007;12:94–8.
119. Cavalcanti A, Shirinzadeh B, Murphy D, Smith JA. Nanorobots for laparoscopic cancer surgery. 6th IEEE/ACIS International Conference on Computer and Information Science (ICIS 2007). Melbourne, Australia, July, 2007.
120. Minton JP. The laser in surgery: a 23-year perspective. Am J Surg 1986;151:725–9.
121. Marcove RC, Miller TR, Cahan WC. The treatment of metastatic bone tumors by freezing. Bull NY Acad Med 1968;44:532–44.
122. Buncker HU, Alpert B, Shah KG. Microvascular grafting. Clin Plast Surg 1978;5:185–94.

EXHIBIT C

American Cancer Society

Cancer Reference Information

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Detailed Guide: Breast Cancer

Chemotherapy

Chemotherapy is treatment with cancer-killing drugs that may be given intravenously (injected into a vein) or by mouth. The drugs travel through the bloodstream to reach cancer cells in most parts of the body. The chemotherapy is given in cycles, with each period of treatment followed by a recovery period. Treatment usually lasts for several months.

When is chemotherapy used?

There are several situations in which chemotherapy may be recommended.

Adjuvant chemotherapy: Systemic therapy given to patients after surgery who have no evidence of cancer spread is called adjuvant therapy. When used as adjuvant therapy after breast-conserving surgery or mastectomy, chemotherapy reduces the risk of breast cancer coming back.

Even in the early stages of the disease, cancer cells may break away from the primary breast tumor and spread through the bloodstream. These cells don't cause symptoms, they don't show up on imaging tests, and they can't be felt during a physical exam. But if they are allowed to grow, they can establish new tumors in other places in the body. The goal of adjuvant chemotherapy is to kill undetected cells that have traveled from the breast.

Neoadjuvant chemotherapy: Chemotherapy given before surgery is called neoadjuvant therapy. The major benefit of neoadjuvant chemotherapy is that it can shrink large cancers so that they are small enough to be removed by lumpectomy instead of mastectomy. Another possible advantage of neoadjuvant chemotherapy is that doctors can see how the cancer responds to chemotherapy. If the tumor does not shrink, your doctor may try different chemotherapy drugs.

So far, it's not clear that neoadjuvant chemotherapy improves survival, but it seems to be at least as effective as adjuvant therapy after surgery.

Chemotherapy for advanced breast cancer: Chemotherapy can also be used as the main treatment for women whose cancer has already spread outside the breast and underarm area at the time it is diagnosed, or if it spreads after initial treatments. The length of treatment depends on whether the cancer shrinks, how much it shrinks, and how a woman tolerates treatment.

How is chemotherapy given?

In most cases (especially for adjuvant and neoadjuvant treatment), chemotherapy is most effective when combinations of more than one drug are used. Many combinations are being used, and it's not clear that any single combination is clearly the best. Clinical studies continue to compare today's most effective treatments against something that may be better.

Some of the most commonly used drug combinations are:

- CMF: cyclophosphamide (Cytoxan), methotrexate (Amethopterin, Mexate, Folex), and 5-fluorouracil (Fluorouracil, 5-FU, Adrucil)
- CAF (FAC): cyclophosphamide, doxorubicin (Adriamycin), and 5-fluorouracil
- AC: doxorubicin (Adriamycin) and cyclophosphamide
- EC: epirubicin (Ellence) and cyclophosphamide
- TAC: docetaxel (Taxotere), doxorubicin (Adriamycin), and cyclophosphamide
- AC → T: doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel (Taxol) or docetaxel (Taxotere)
- A → CMF: doxorubicin (Adriamycin), followed by CMF
- CEF (FEC): cyclophosphamide, epirubicin, and 5-fluorouracil (with or without docetaxel)
- TC: docetaxel (Taxotere) and cyclophosphamide
- GT: gemcitabine (Gemzar) and paclitaxel (Taxol)

Some other chemotherapy drugs used for treating women with breast cancer include carboplatin (Paraplatin), cisplatin (Platinol), vinorelbine (Navelbine), capecitabine (Xeloda), pegylated liposomal doxorubicin (Doxil), ixabepilone (Ixempra), and albumin-bound paclitaxel (Abraxane).

Doctors give chemotherapy in cycles, with each period of treatment followed by a rest period. The chemotherapy begins on the first day of each cycle, and then the body is given time to recover from the effects of chemotherapy. The chemotherapy drugs are then repeated to start the next cycle. The time between giving the chemotherapy drugs is generally 2 or 3 weeks and varies according the specific chemotherapy drug or combination of drugs. Some drugs are given more often. These cycles generally last for a total time of 3 to 6 months when given as adjuvant therapy, depending on the drugs used. Treatment may be longer for advanced breast cancer.

Possible side effects

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects. Some women have many side effects while other women may have few.

The side effects of chemotherapy depend on the type of drugs, the amount taken, and the length of treatment. Some of the most common possible side effects include:

- hair loss
- mouth sores
- loss of appetite
- nausea and vomiting
- increased chance of infections (due to low white blood cell counts)

- easy bruising or bleeding (due to low blood platelet counts)
- fatigue (due to low red blood cell counts and other reasons)

These side effects are usually short-term and go away after treatment is finished. It's important to let your health care team know if you have any side effects, as there are often ways to lessen them. For example, drugs can be given to help prevent or reduce nausea and vomiting.

Several other side effects are also possible. Some of these are only seen with certain chemotherapy drugs. Your cancer care team will give you information about the possible side effects of the specific drugs you are getting.

Menstrual changes: For younger women, changes in menstrual periods are another possible side effect of chemotherapy. Premature menopause (not having any more menstrual periods) and infertility (not being able to become pregnant) are possible permanent complications of chemotherapy. Some chemotherapy drugs are more likely to do this than others. The older a woman is when she receives chemotherapy, the more likely it is that she will become infertile or menopausal as a result. When this happens, it can also lead to rapid bone loss from osteoporosis. Again, there are medicines that can help prevent this possible side effect.

You cannot depend on chemotherapy to prevent pregnancy, and getting pregnant while receiving chemotherapy could lead to birth defects and interfere with treatment. For this reason, it is important that pre-menopausal women who are sexually active discuss using birth control with their doctor. It is safe to have children after chemotherapy, but it's not safe to get pregnant while on treatment.

Neuropathy: Several drugs used to treat breast cancer, including the taxanes (docetaxel and paclitaxel), platinum agents (carboplatin, cisplatin), and ixabepilone, can damage nerves outside of the brain and spinal cord. This can sometimes lead to symptoms (mainly in the hands and feet) such as pain, burning or tingling sensations, sensitivity to cold or heat, or weakness. In most cases this goes away once treatment is stopped, but it may be long-lasting in some women.

Heart damage: Adriamycin (doxorubicin) and some other drugs may cause permanent heart damage if used for a long time or in high doses. For this reason, doctors carefully control the doses and use echocardiograms or other heart tests to monitor heart function. Treatment with these drugs will be stopped at the first sign of heart damage.

Chemobrain: Another possible side effect of chemotherapy is "chemobrain." Many women who get chemotherapy for breast cancer report a slight decrease in mental functioning. There may be some problems with concentration and memory, which may last a long time. Still, most women do function well after chemotherapy. In studies that have found chemobrain to be a side effect of treatment, the symptoms most often go away within a few years. For more information, see the separate American Cancer Society document, *Chemobrain*.

Increased risk of leukemia: Very rarely, certain chemotherapy drugs may cause acute myeloid leukemia, a life-threatening cancer of white blood cells. When this happens it is usually within 10 years after treatment. In most women, chemotherapy's benefits in preventing breast cancer from coming back or in extending life are likely to far exceed the risk of this serious but rare complication.

Feeling unwell or tired: Many women do not feel as healthy after receiving chemotherapy as they did before. There is often a residual feeling of body pain or achiness and a mild loss of physical functioning. These are very subtle changes that are only revealed by closely questioning women who have undergone chemotherapy.

Fatigue is another common (but often overlooked) problem for women who have received chemotherapy. This may last up to several years. It can often be helped, so it is important to let your doctor or nurse know about it. Exercise, naps, and conserving energy may be recommended. If there are problems with sleep, these can be treated. Sometimes there is depression, which may be helped by counseling and/or medicines.

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EXHIBIT D

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Dictionary of Cancer Terms

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micrometastasis (MY-kroh-meh-TAS-tuh-sis)

Small numbers of cancer cells that have spread from the primary tumor to other parts of the body and are too few to be picked up in a screening or diagnostic test.

Previous Definitions: MG98, MGUS, microcalcification, microfluidic device, microgram

Next Definitions: micromolar, micronutrient, microorganism, microsatellite, microsatellite instability